REMARKS

Claims 5 and 9-19 were pending. Claim 18 has been canceled herein without prejudice. Claims 12, 17, and 19 have been amended herein. Claim 12 has been amended to include the molecular weight recitations from canceled claim 18. Claim 17 has been amended to depend upon claim 16. Claim 19 has been amended to delete the phrase "at least one" in reference to complementary determining regions. No new matter is added thereby.

Preliminarily, Applicants acknowledge with appreciation the withdrawal of the rejection of claims 9-12 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

Rejection Under 35 U.S.C. § 102(b)

In the official action, the Examiner maintained the rejection of claims 5, 11, and 12 as allegedly anticipated by Zapata et al. (FASEB J. 9:A1479, 1995 "Zapata[a]"). Applicants respectfully traverse this rejection.

Claim 12 has been amended to include the molecular weight recitations of previous claim 18. Previous claim 18 was not rejected over Zapata[a]. Amended claim 12 recites that the polymer attached to the antibody has a molecular weight from 25,000Da to 40,000Da. Zapata[a] reports "the pharmacokinetic effect of 5kDa and 10kDa MePEG chains attached to a sulfhydryl group in the hinge region of a monoclonal Fab' fragment". Zapata[a] does not disclose or suggest polymers of from 25,000 to 40,000 Da. Amended claim 12 and dependent claims 5 and 11 are thus novel over Zapata[a].

Applicants request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

The Examiner maintained the rejection of claims 5 and 9-12, adding claims 13-17 and 19, as allegedly obvious in view of Zapata[a] as applied to claims 5, 11, and 12, further in view of Zapata[b] (U.S. Pat. 6,214,984, continuation date of 4/20/95). Applicants respectfully traverse this rejection.

Zapata[b] describes methods for preparing antibody fragments. Specifically, it provides greater detail regarding the production of the anti-CD18 Fab' fragment described in Zapata[a], including sequence information. Zapata[b], however, does not disclose or suggest the attachment of a polymer of from 25,000Da to 40,000Da to the Fab' fragment, as recited in amended claim 12. Since neither Zapata[a] and Zapata[b] discloses or suggests attaching a

polymer having a molecular weight as presently recited in amended claim 12 to an antibody, amended claim 12 is not rendered obvious by a combination of Zapata[a] and Zapata[b]. The remaining claims rejected depend from claim 12.

Applicants respectfully request that this rejection be withdrawn.

The Examiner also maintained the rejection of claims 5 and 9-12, adding claims 13-17 and 19, as allegedly obvious in view of Jacobs and Bodmer. Applicants respectfully traverse this rejection.

Jacobs describes PEGylated antibody fragments for the treatment of insulin dependent diabetes. In particular, Jacobs reports the attachment of PEG to free sulfhydryl groups in the hinge region of Fab' fragments. Bodmer describes an altered Fab' fragment having a hinge region, which has a different number of cysteine residues. The Examiner alleges that it would have been obvious to produce an altered Fab' fragment having a single cysteine residue in the hinge region as described by Bodmer with a polymer attached to it as described by Jacob.

Jacobs, however, only describes the attachment of a polymer with a molecular weight of 200-8,000Da. Amended claim 12 recites the attachment of a polymer of from 25,000 to 40,000Da. Even if the ordinary skilled person were to produced an altered Fab ' fragment as described by Bodmer, and to attach a polymer as described by Jacob, the result would not yield a modified Fab' fragment as set forth in claim 12. The remaining claims depend from claim 12.

Applicants respectfully request that this rejection be withdrawn.

New Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner rejected claim 17 as allegedly indefinite for referring to "the soluble antigen" of claim 19 because there was insufficient antecedent basis for the recitation. Claim 17 has been amended herein to depend from claim 16 This rejection has been overcome.

Applicants request that this rejection be withdrawn.

New Rejection Under 35 U.S.C. § 112, first paragraph

The Examiner rejected claim 19 on the basis that the specification allegedly only enables the skilled person to produce a polymer modified antibody fragment wherein all six complementarity determining regions ("CDRs") are from one antibody and the framework regions are from a second antibody. Claim 19 has been amended to clarify that all the CDRs are from one antibody.

Applicants request that this rejection be withdrawn.

New Rejection Under 35 U.S.C. § 103(a)

The Examiner rejected claims 5 and 9-19 as allegedly unpatentable over Zapata[a], Zapata[b], and Faanes et al. (U.S. Pat. 5,695,760, filed 4/95). Applicants respectfully traverse this rejection.

Faanes et al. describes the production of modified anti-ICAM-1 antibodies for the treatment of inflammation. Column 12, lines 60-65 reports that, although activated mPEG of molecular weight 5kDa is the most preferred agent, activated mPEG of up to 40kDa molecular weight may be used. The Examiner asserts that there would have been motivation to replace the polymer of Zapata[a] with a polymer having a higher molecular weight in view of Faanes et al. to improve clearance rates, particularly considering the therapeutic applications for the anti-CD18 antibodies of Zapata[b]. The Examiner alleged that the skilled person would have been motivated to make such a change due to the fact that the use of the 10kDa polymer in Zapata[a] resulted in better clearance compared to the use of the 5kDa polymer.

It is clear from Zapata[a] that polymers of 5kDa and 10kDa were used to modify the Fab' fragments in order increase the half-life of the fragment **without** affecting antigen binding. As reported in Zapata[a], although higher levels of PEG modification resulted in a longer circulatory half-life, this was accompanied by a **loss** in antigen-binding activity (see, for example, p1128-29 of Pedley *et al,* 1994, *Br J. Cancer*, 70: 1126-30, which was cited earlier in prosecution). The skilled person would **not,** therefore, have been motivated to increase the molecular weight of the polymer in Zapata [a] from 10kDa to from 25,000 to 40,000Da and, if motivated, would not have had a reasonable expectation of success . A modified antibody with reduced clearance rate is of no use therapeutically or otherwise if it cannot bind its target antigen.

Faanes et al. does not provide any teaching which would dispel the prejudice in Zapata[a] against using high molecular weight polymers to modify antibodies. Faanes et al. describes modifying antibodies by attaching multiple polymer molecules. Faanes et al. does not teach modifying antibodies by attaching polymers to the hinge region, much less cysteines, much less the attachment of a single polymer to a single cysteine in the hinge region. Indeed, Faanes et al. reports , at column 11, lines 48-53, using "activated PEG derivatives" which target amines such as lysines. As set forth on page 2, lines 16-23 of the above-identified application as filed,

random attachment of PEG to lysine residues is not suitable, as it often leads to impairment of function of the protein. The skilled person would not therefore have had been motivated to combine Zapata[a] and Faanes et al.

Furthermore, although Faanes et al. reports that an antibody was derivatized with 20,000 MW analogs of SCM-PEG and SPA-PEG , it reports that these and other coupling chemistries were "tried" at 40,000 MW (see column 22, lines 52-58). The skilled person, thus, would not have had a reasonable expectation of success of preparing an Fab' with a polymer having a molecular weight according to the present invention, much less that the Fab' so prepared would increase retention time without altering antigen binding. Surprisingly, the current application discloses, in Example 2, that Fab' fragments modified with PEG of 25,000Da and 40,000Da according to the present invention did not result in a decrease in antigen binding, while the Fab' fragment modified with 25,000Da PEG randomly did (see Figure 4). The subject matter of the amended claims is thus inventive over Zapata[a] and [b] and Faanes et al.

Applicants respectfully request that this rejection be withdrawn.

Applicants respectfully submit that the application is in condition for allowance and request early notification of same. If the Examiner disagrees, or feels a telephonic interview would be helpful, she is asked to contact the undersigned at 215-665-5593 to discuss.

Respectfully submitted,

Date: April 30, 2003

Doreen Yatko Trujillo
Registration No. 35,719

COZEN O'CONNOR, P.C.
1900 Market Street, 6th Floor
Philadelphia, PA 19103-3508
(215) 665-5593 - Telephone
(215) 701-2005 - Facsimile